

**AMENDMENTS TO THE CLAIMS**

**This listing of claims will replace all prior versions and listings of claims in the application:**

**LISTING OF CLAIMS:**

1. (currently amended): An aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the form of micelles in the composition, and a biologically active compound having a measured and/or calculated partition coefficient between octanol and water of at least 1.5 associated hydrophobically with the copolymer in the core of the micelles, wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers comprising a zwitterionic monomer whereby the hydrophilic block has pendant zwitterionic groups; wherein the hydrophobic block is formed by radical polymerisation of ethylenically unsaturated monomers.

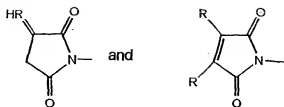
wherein the degree of polymerisation of the hydrophilic block is in the range 10 to 100, the degree of polymerisation of the hydrophobic block is in the range 10 to 250, and the degree of polymerisation of the hydrophilic to hydrophobic block is in 1: (5-1) and wherein hydrophobic block is formed from (diisopropyl-amino)ethyl methacrylate.

2. - 6. (canceled).

7. (previously presented): A composition according to claim 1 in which the zwitterionic monomer has the general formula

Y B X                      I

in which Y is an ethylenically unsaturated group selected from the group consisting of  $H_2C=CR-CO-A$ ,  $H_2C=CR-C_6H_4-A^1$ ,  $H_2C=CR-CH_2A^2$ ,  $R^2O-CO-CR=CR-CO-O$ ,  $RCH=CH-CO-O$ ,  $RCH=C(COOR^2)CH_2-CO-O$ ,



A is -O- or NR<sup>1</sup>;

A<sup>1</sup> is selected from the group consisting of a bond, (CH<sub>2</sub>)<sub>1</sub>A<sup>2</sup> and (CH<sub>2</sub>)<sub>1</sub>SO<sub>3</sub><sup>-</sup> in which 1 is 1 to 12;

A<sup>2</sup> is selected from the group consisting of a bond, -O-, O-CO-, CO-O, CO-NR<sup>1</sup>-, -NR<sup>1</sup>-CO, O-CO-NR<sup>1</sup>-, and NR<sup>1</sup>CO-O-;

R is hydrogen or C<sub>1-4</sub> alkyl;

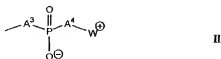
R<sup>1</sup> is hydrogen, C<sub>1-4</sub> alkyl or BX;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub>, alkyl;

B is selected from the group consisting of a bond, straight and branched alkanediyl groups, alkylene oxalkylene groups, and alkylene (oligooxalkylene) groups, optionally containing one or more fluorine substituents; and

X is a zwitterionic group.

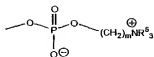
8. (previously presented): A composition according to claim 7 in which X is a group of the general formula II



in which the moieties A<sup>3</sup> and A<sup>4</sup>, which are the same or different, are -O-, -S-, -NH- or a valence bond and W<sup>+</sup> is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is a C<sub>1-12</sub>-alkanediyl group.

9. (previously presented): A composition according to claim 7 in which X has the

general formula III



III

where the groups  $R^5$  are the same or different and each is hydrogen or  $C_{1-4}$  alkyl, and  $m$  is from 1 to 4.

10. (previously presented): A composition according to claim 7 in which  $Y$  is  $H_2C=CR-CO-A-$  in which  $R$  is H or methyl and  $-A-$  is  $-O-$  or  $-NH-$ .

11. (previously presented): A composition according to claim 7 in which  $B$  is a  $C_{2-6}$ -alkanediy group.

12. (previously presented): A composition according to claim 7 in which the zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

13. - 19. (canceled).

20. (previously presented): A composition according to claim 1 in which the polydispersity of molecular weight of each of the blocks is less than 2.0.

21. - 23. (canceled).

24. (previously presented): A composition according to claim 1 in which the radical polymerisation is a controlled radical polymerisation.

25. (original): A composition according to claim 24 in which the polymerisation is an atom transfer radical polymerisation or group transfer polymerisation.

26. (original): A composition according to claim 25 in which the initiator for the radical transfer polymerisation process is a polymer compound in which the polymeric moiety is hydrophobic which forms the hydrophobic block of the copolymer.

27. (original): A composition according to claim 25 in which the hydrophobic block is also formed from ethylenically unsaturated monomers by a radical transfer polymerisation process.

28. (previously presented): A composition according to claim 1 in which the biologically active molecule is a cytotoxic compound.

29. (withdrawn): A method of forming an aqueous composition comprising an amphiphilic block copolymer and a biologically active compound, in which the copolymer comprises a hydrophilic block and a hydrophobic block in which process an aqueous dispersion of empty copolymer micelles is formed and the micellar dispersion is contacted with biologically active compound under conditions such that the biologically active compound becomes associated with the copolymer in the micelles, wherein the hydrophilic block has pendant zwitterionic groups.

30. (withdrawn): A method according to claim 29 in which the biologically active compound has a partition coefficient between octanol and water of at least 1.0.

31. (withdrawn): A method according to claim 29 in which the hydrophobic block of the copolymer comprises ionisable groups, and in which the empty copolymer micelles are formed by a process comprising:

a) a first copolymer dissolution step in which the block copolymer, with the groups of hydrophobic block in at least partially ionised form, is dissolved in an aqueous liquid, and

b) a second micelle forming step in which the conditions in the solution are adjusted so that the ionised groups are converted at least partially to their ionisable form, whereby the copolymer is above the critical micelle concentration in the aqueous liquid and micelles are formed.

32. (withdrawn): A method according to claim 31 in which the conditions which are

adjusted are of temperature and/or pH.

33. (withdrawn): A method according to claim 31 in which the ionisable groups are primary, secondary or tertiary amine groups and in which the micelle forming step involves raising the pH whereby the ionised groups become deprotonated.

34. (withdrawn): A method according to claim 29 in which the biologically active compound is in solid form when it is contacted with the aqueous dispersion of empty micelles.

35. (withdrawn): A method according to claim 29 in which the biologically active compound is in solution in an organic solvent when it is contacted with the aqueous dispersion of empty micelles.

36 - 37. (canceled).

38. (previously presented): A composition according to claim 8 in which  $W^+$  is a group of formula

$-W^1-N^+R^3_3$ ,  $-W^1-P^+R^4_3$ ,  $-W^1-S^+R^4_2$  or  $-W^1-Het^+$  in which:

$W^1$  is selected from the group consisting of alkanediyl of 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene and alkylene cycloalkyl alkylene, which group  $W^1$  optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups  $R^3$  are the same or different and each is selected from the group consisting of hydrogen, alkyl of 1 to 4 carbon atoms and aryl or two of the groups  $R^3$  together with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or the three groups  $R^3$  together with the nitrogen atom to which they are attached as heteroaromatic ring having 5 to 7 atoms, either of which rings may be fused with another saturated or unsaturated ring to form a fused ring structure containing from 5 to 7 atoms

in each ring, and optionally one or more of the groups  $R^3$  is substituted by a hydrophilic functional group, and

the groups  $R^4$  are the same or different and each is  $R^3$  or a group  $OR^3$ , where  $R^3$  is as defined above; and

Het is an aromatic nitrogen-, phosphorus- or sulphur-containing ring.

39 - 41. (canceled).

42. (previously presented): A composition according to claim 20 in which the said polydispersity is in the range 1.1 to 1.4.

43. - 44. (canceled).

45. (withdrawn): A method according to claim 29 in which the biologically active molecule is a cytotoxic compound.

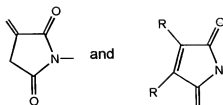
46. (withdrawn): A method according to claim 29 wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers.

47. (withdrawn): A method according to claim 46 in which the monomers comprise a zwitterionic monomer.

48. (withdrawn): A method according to claim 47 in which the zwitterionic monomer has the general formula

$YBX$   $I$

in which Y is an ethylenically unsaturated group selected from the group consisting of  $H_2C=CR-CO-A-$ ,  $H_2C=CR-C_6H_4-A^1-$ ,  $H_2C=CR-CH_2A^2$ ,  $R^2O-CO-CR=CR-CO-O$ ,  $RCH=CH-CO-O-$ ,  $RCH=C(COOR^2)CH_2-CO-O$ ,



A is -O- or NR<sup>1</sup>;

A<sup>1</sup> is selected from the group consisting of a bond, (CH<sub>2</sub>)<sub>l</sub>A<sup>2</sup> and (CH<sub>2</sub>)<sub>l</sub>SO<sub>3</sub><sup>-</sup> in which l is 1 to 12;

A<sup>2</sup> is selected from the group consisting of a bond, -O-, O-CO-, CO-O, CO-NR<sup>1</sup>-, -NR<sup>1</sup>-CO, O-CO-NR<sup>1</sup>- and NR<sup>1</sup>-CO-O-;

R is hydrogen or C<sub>1-4</sub> alkyl;

R<sup>1</sup> is hydrogen, C<sub>1-4</sub>-alkyl or BX;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl; and

B is selected from the group consisting of a bond, straight and branched alkanediyl groups, alkylene oxalkylene groups, and alkylene (oligooxalkylene) groups, optionally containing one or more fluorine substituents.

49. (withdrawn): A method according to claim 49 in which W<sup>+</sup> is a group of formula -W<sup>1</sup>-N<sup>+</sup>R<sup>3</sup><sub>3</sub>, -W<sup>1</sup>-P<sup>+</sup>R<sup>4</sup><sub>3</sub>, -W<sup>1</sup>-S<sup>+</sup>R<sup>4</sup><sub>2</sub> or -W<sup>1</sup>-Het<sup>+</sup> in which:

W<sup>1</sup> is selected from the group consisting of alkanediyl of 2-6 carbon atoms optionally containing one or more ethylenically unsaturated double or triple bonds, disubstituted-aryl (arylene), alkylene arylene, arylene alkylene, alkylene aryl alkylene, cycloalkanediyl, alkylene cycloalkyl, cycloalkyl alkylene and alkylene cycloalkyl alkylene, which group W<sup>1</sup> optionally contains one or more fluorine substituents and/or one or more functional groups; and

either the groups R<sup>3</sup> are the same or different and each is selected from the group consisting of hydrogen, alkyl of 1 to 4 carbon atoms and aryl or two of the groups R<sup>3</sup> together

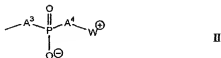
with the nitrogen atom to which they are attached form an aliphatic heterocyclic ring containing from 5 to 7 atoms, or

the three groups  $R^3$  together with the nitrogen atom to which they are attached as heteroaromatic ring having 5 to 7 atoms, either of which rings may be fused with another saturated or unsaturated ring to form a fused ring structure containing from 5 to 7 atoms in each ring, and optionally one or more of the groups  $R^3$  is substituted by a hydrophilic functional group, and

the groups  $R^4$  are the same or different and each is  $R^3$  or a group  $OR^3$ , where  $R^3$  is as defined above; and

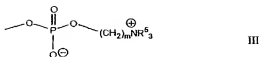
Het is an aromatic nitrogen-, phosphorus- or sulphur-containing ring.

50. (withdrawn): A method according to claim 49 in which X is a group of the general formula II



in which the moieties  $A^3$  and  $A^4$ , which are the same or different, are -O-, -S-, -NH- or a valence bond and  $W^+$  is a group comprising an ammonium, phosphonium or sulphonium cationic group and a group linking the anionic and cationic moieties which is a  $C_{1-12}$ -alkanediyl group.

51. (withdrawn): A method according to claim 48 in which X has the general formula III



where the groups  $R^5$  are the same or different and each is hydrogen or  $C_{1-4}$  alkyl, and m is from 1



to 4.

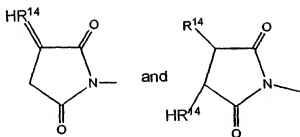
52. (withdrawn): The method according to claim 48 in which the zwitterionic monomer is 2-methacryloyloxyethyl-2'-trimethylammonium ethyl phosphate inner salt.

53. (withdrawn): A method according to claim 29 in which the hydrophobic block comprises pendant groups which are ionisable, having a  $pK_A$  or  $pK_B$  in the range 4 to 10.

54. (withdrawn): A method according to claim 53 in which the hydrophobic block is formed by radical polymerisation of ethylenically unsaturated monomers including monomers having the general formula VII



in which  $Y^1$  is an ethylenically unsaturated group selected from the group consisting of  $H_2C=CR^{40}-CO-A^8$ -,  $H_2C=CR^{14}-C_6H_4-A^9$ -,  $H_2C=CR^{14}-CH_2A^{10}$ ,  $R^{16}O-CO-CR^{14}=CR^{14}-CO-O$ ,  $R^{14}CH=CH-CO-O$ -,  $R^{14}CH=C(COOR^{16})CH_2-CO-O$ ,



$A^8$  is  $-O-$  or  $NR^{15}$ ;

$A^9$  is selected from the group consisting of a bond,  $(CH_2)_qA^{10}$  and  $(CH_2)_qSO_3-$  in which  $q$  is 1 to 12;

$A^{10}$  is selected from the group consisting of a bond,  $-O-$ ,  $O-CO-$ ,  $CO-O-$ ,  $CO-NR^{41}-$ ,  $-NR^{41}-CO$ ,  $O-CO-NR^{15}-$  and  $NR^{15}-CO-O-$ ;

$R^{14}$  is hydrogen or  $C_{1-4}$  alkyl;

$R^{15}$  is hydrogen,  $C_{1-4}$ -alkyl or  $B^1Q$ ;

$R^{16}$  is hydrogen or  $C_{1-4}$  alkyl;

$B^1$  is selected from the group consisting of a bond, straight and branched alkanediyl groups, alkylene oxalkylene groups, and alkylene (oligooxalkylene) group, optionally containing one or more fluorine substituents; and

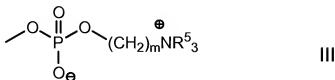
Q is a cationic or cationisable group of the formula  $-NR^{17}_p$ ,  $-PR^{17}_p$  or  $SR^{17}_p$ , in which p is 2 or 3, r is 1 or 2, the groups  $R^{17}$  are the same or different and each is selected from the group consisting of hydrogen,  $C_{1-24}$  alkyl and aryl, or two of the groups  $R^{17}$  together with the heteroatom to which they are attached from a 5 to 7 membered heterocyclic ring or three  $R^{17}$  groups together with the heteroatom to which they are attached form a 5 to 7 membered heteroaromatic ring, either of which rings may be fused to another 5 to 7 membered saturated or unsaturated ring, and any of the  $R^{17}$  groups may be substituted by amino or hydroxyl groups or halogen.

55. (withdrawn): A method according to claim 54 in which Q is  $NR^{17}_2$  in which each  $R^{17}$  is H or  $C_{1-4}$  alkyl.

56. (withdrawn): A method according to claim 46 in which the radical polymerisation is a controlled radical polymerisation.

57. (currently amended): An aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the form of micelles in the composition and a biologically active compound having a measured and/or calculated partition coefficient between octanol and water of at least 1.5 associated with the copolymer in the core of the micelles, wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers comprising a zwitterionic monomer of the formula 1 whereby the block has pendant zwitterionic groups

wherein Y is  $\text{H}_2\text{C}=\text{CR}-\text{CO}-\text{A}$ , R is H or  $\text{C}_{1-4}$  alkyl A is O or NH, B is a  $\text{C}_{2-6}$  alkanediyl group, and X has general formula III



wherein the group  $\text{R}^5$  are the same or different and each is H or  $\text{C}_{1-4}$  alkyl and M is from 1 to 4,

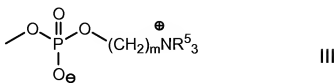
~~and~~ wherein the polymerisation is an atom transfer radical polymerisation or group transfer polymerisation carried out in the presence of an atom transfer or group transfer initiator that is a polymer compound in which the polymeric moiety is hydrophobic and forms the hydrophobic block of the copolymer; and

wherein the biologically active compound is a cytotoxic compound.

58. (currently amended): An aqueous composition comprising an amphiphilic block copolymer having a hydrophilic block and a hydrophobic block, dispersed in the form of micelles in the composition and a biologically active compound having a measured and/or calculated partition coefficient between octanol and water of at least 1.5 associated with the copolymer in the core of the micelles, wherein the hydrophilic block is formed by radical polymerisation of ethylenically unsaturated monomers comprising a zwitterionic monomer of the formula I whereby the block has pendant zwitterionic groups



wherein Y is  $\text{H}_2\text{C}=\text{CR}-\text{CO}-\text{A}$ , R is H or  $\text{C}_{1-4}$  alkyl A is O or NH, B is a  $\text{C}_{2-6}$  alkanediyl group, and X has general formula III



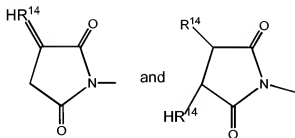
wherein the group  $R^5$  are the same or different and each is H or  $C_{1-4}$  alkyl and M is from 1 to 4,

wherein the degree of polymerisation in the hydrophobic block I in the range 2 to 1000,

and wherein the block comprises pendant groups which are ionisable, having a  $pK_A$  or  $pK_B$  in the range 4 to 10 and is formed by radical polymerisation of ethylenically unsaturated monomers having the general formula VII



in which  $Y^1$  is an ethylenically unsaturated group selected from the group consisting of  $H_2C=CR^{40}-CO-A^8$ ,  $H_2C=CR^{14}-C_6H_4-A^9$ ,  $H_2C=CR^{14}-CH_2A^{10}$ ,  $R^{16}O-CO-CR^{14}=CR^{14}-CO-O$ ,  $R^{14}CH=CH-CO-O$ ,  $R^{14}CH=C(COOR^{16})CH_2-CO-O$ ,



$A^8$  is  $-O-$  or  $NR^{15}$ ;

$A^9$  is selected from the group consisting of a bond,  $(CH_2)_qA^{10}$  and  $(CH_2)_qSO_3^-$  in which q is 1 to 12;

A<sup>10</sup> is selected from the group consisting of a bond, -O-, O-CO-, CO-O-, CO-NR<sup>41</sup>-, -NR<sup>41</sup>-CO, O-CO-NR<sup>15</sup>-, NR<sup>15</sup>-CO-O-;

R<sup>14</sup> is hydrogen or C<sub>1-4</sub> alkyl;

R<sup>15</sup> is hydrogen, C<sub>1-4</sub> alkyl or B<sup>1</sup>Q;

R<sup>16</sup> is hydrogen or C<sub>1-4</sub> alkyl;

B<sup>1</sup> is selected from the group consisting of a bond, straight and branched alkanediyl groups, alkylene oxalkylene groups, and alkylene (oligooxalkylene) groups, optionally containing one or more fluorine substituents; and

Q is NR<sup>17</sup><sub>2</sub> in which each R<sup>17</sup> is H or C<sub>1-4</sub> alkyl,

wherein the degree of polymerisation of the hydrophobic block is in the range 5 to 2000; ~~and~~

wherein the ratio of the degrees of polymerisation of the hydrophobic to hydrophilic blocks is in the range 1:5 to 10:1; and

wherein the biologically active compound is a cytotoxic compound.

59 - 60. (cancelled).

61. (new): An aqueous composition comprising an amphiphilic block copolymer, having a hydrophilic block and a hydrophobic block, dispersed in the solution and a cytotoxic active compound non-covalently associated with the polymer, wherein the hydrophilic block is formed from 2-methylacryloyl-oxyethyl 1-2'-trimethylammonium ethyl phosphate inner salt and has a degree of polymerisation in the range 10 to 100, the hydrophobic block is formed from 2-(diisopropyl-amino)ethyl methacrylate and has a degree of polymerisation in the range 10 to 250, and the ratio of the degrees of polymerisation of hydrophilic to hydrophobic blocks is in the range 0.2 to 1.